IV. REMARKS

Examiner objects to the disclosure on the ground that it contains an embedded hyperlink and/or other form of browser-executable code. Office Action, p. 3. In response to the Examiner's objection, the specification has been amended by deleting the embedded hyperlink and/or other form of browser-executable code. No new matter has been added.

Claims 28-31 and 61-158, which are drawn to non-elected inventions, have been canceled, without prejudice to pursue the subject matter in a related application. After entry of this amendment, claims 1-27 and 32-60 will be pending.

A. The Claimed Invention

The invention relates to collections of lines of transgenic animals that express a gene coding a selectable or detectable marker (a "system gene") in a different subset of cells by virtue of being regulated by regulatory sequences of an endogenous gene (termed a "characterizing gene"). The invention provides a method to mark certain populations of cells in each member strain of the collection so that those cells can be detected and/or isolated. The transgenic animals of the invention are not intended to have an altered physiological phenotype, but rather to provide otherwise normal animals from which a population of cells may be identified or isolated for further manipulation. In particular, claim 1 is directed to a collection of two or more lines of transgenic animals comprising a transgene, said transgene comprising first sequences, the system gene, coding for a selectable or detectable marker protein operably linked to a regulatory sequence of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene so that the expression pattern of first sequence is substantially the same as the expression pattern of the said endogenous gene. Claims 2-27 are dependent on claim 1. Claim 32 claims a method of making a collection of two or more lines of transgenic animals comprising a transgene of the invention. Claims 33-60 are dependent on claim 32.

B. Rejection Under 35 U.S.C. § 112, First Paragraph For Lack of Enablement Should be Withdrawn

Claims 1-27 and 32-60 are rejected under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. The Examiner states that methods for generating transgenic animals as described in the specification are generally known in the art and the specification fully enables the insertion of a polynucleotide into an animal of interest. Office Action, p. 9.

However, the Examiner alleges that the specification is not enabling because (1) the specification fails to provide the regulatory sequences of characterizing genes, (2) the specification does not provide evidence that the characterizing gene regulates the system gene to have the same expression pattern as the endogenous gene, and (3) because the behavior of transgenes is unpredictable. Office Action, p. 5-10. Applicant respectfully traverses the rejection.

The enablement requirement of 35 U.S.C. § 112 is met when in view of the specification and what is known in the art, practicing the invention does not require undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been explained in *In re Wands*, 8 U.S.P.Q.2d at 1404. Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. *Id.* The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine or the specification provides reasonable amount of guidance and direction to the experimentation. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Pat. Bd. App. 1982); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Where a disclosure provides considerable direction and guidance on how to practice the invention, and where, at the time of application, the skill in the art was quite high and the methods need to practice the invention well known, a conclusion of enablement should be made. *In re Wands*, 8 U.S.P.Q.2d at 1406. In the present case, as set forth below, the disclosure does provide sufficient direction and guidance, the skill in the art is high, and the methods to practice the invention are well known; thus, the claims are enabled.

1. <u>Specification Is Enabling for Promoters of Characterization Genes</u>

The Examiner alleges that the specification is not enabling because it does not teach the specific promoter sequences for each of the characterizing genes. Office Action, pp. 5 and 10. Specifically, the Examiner alleges that promoters of characterizing genes are starting material required to practice the invention and, thus, under *Genetech, Inc. v. Novo Nordisk a/S*, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997), the specification is not enabling. Office Action, p. 7. The Examiner also alleges that the specification fails to enable dependent

claims that recite specific pathways and specific phenotypes with which characterizing genes are associated with because the specification does not teach specific genes that are responsible for producing specific phenotypes and the specification does not provide description of these genes or means to isolate and use these genes within the context of the claims. Office Action, pp. 8-9. Applicant respectfully disagrees.

The characterizing gene of the invention is a gene endogenous to a host cell or host organism or is an ortholog of the endogenous gene. Specification, p. 21, ll. 9-11; Pub. App. at ¶ 154.[1] The expression or non-expression this endogenous gene characterizes the particular cells of interest. Specification, p. 21, ll. 12-15; Pub. App. at ¶ 154. The transgene of the present invention comprises a characterizing gene operably linked to a system gene that codes for a marker so that the expression pattern of the system gene is substantially the same (as defined in the specification) as the expression pattern of the endogenous characterizing gene. Specification, p. 2, ll. 12-18; Pub. App. at ¶ 154. Since the expression of the marker is the same as the expression pattern of the endogenous characterizing gene, the present invention provides for cells of interest, *i.e.*, those expressing the endogenous characterizing gene, to be detected, isolated, and/or selected from other cells of the transgenic animal or explanted tissue thereof. *Id.*

The specification teaches that the transgene of the invention comprises all or a portion of the genomic sequence of the characterizing gene, particularly the sequences 5' of the coding sequence that contain the regulatory sequences. Specification, p. 19, ll. 3-5; Pub. App. at ¶ 148. The specification discloses that the characterizing gene genomic sequences are preferably in a vector that can encompass large lengths of sequence, such as cosmids, YACs, and BACs that encompass 50 to 300 kb of sequence. Specification, p. 19, ll. 9-13; Pub. at ¶ 149. The larger the sequence length, the more likely that the vector contains sufficient regulatory sequences from the characterizing gene to direct expression of the system gene coding sequences in substantially the same pattern as the endogenous characterizing gene. Specification, p. 19, ll. 13-14; Pub. App. at ¶ 149. Methods to determine whether a vector contains sufficient regulatory sequences from the characterizing gene are known in the art, such as by sequencing, restriction mapping, and PCR amplification assays. Specification, p. 19, l. 18 to p. 20, l. 9; Pub. App. at ¶ 149. The specification also provides by way of example how to produce and use a BAC clone of the invention in Section 5. Thus, the specification provides sufficient guidance to one of ordinary skill in the art to

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[1] "Pub. App.", as used herein, refers to Published Application US 2003/0051266

produce transgenes of the invention comprising sufficient regulatory sequences of characterizing genes although the specification does not disclose the specific regulatory sequences of each characterizing gene.

The specification further teaches that the regulatory sequences, *e.g.*, a promoter and/or enhancer, of the characterizing genes are either known in the art or can be determined by using methods known in the art. Specification, p. 59, l. 31 to p. 60, l. 2; Pub. App. at ¶ 180. As the Examiner notes, the specification lists numerous genes that may be used as characterizing genes, but the promoters of these genes are not disclosed. Office Action, p. 5 and Specification, Section 4.2.1. The specification does not disclose the specific regulatory sequence of each of these known genes because the regulatory sequence can be obtained by one of skill in the art, such as from one of the publicly available databases listed in the specification (see specification, p. 22, lines 3-31; Pub. App. ¶ 157-160), references (see specification, p. 57, l. 31 to p. 58, l. 22; Pub. App. ¶ 176), and/or by a method known in the art (see specification, Section 5, especially Section 5.1.2). One skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). In fact, well known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 94 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art"). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 6 U.S.P.Q.2d 1065 (D. Del. 1991). Therefore, since the regulatory sequences of characterizing genes of the invention are known in the art, it cannot be said that the specification is non-enabling because it does not list the specific regulatory sequences of characterizing genes.

The Examiner also alleges that the specification is non-enabling because it fails to provide promoters of characterizing genes which provide the required expression pattern and cites to *Genentech, Inc. v. Novo Nordisk a/S*, 42 U.S.P.Q.2d 1001 (Fed. Cir. 1997). Office Action, p. 7. In *Genentech*, the court states that "when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried, undue experimentation is required; there if a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process

is within the skill of the art." *Genentech,* 42 U.S.P.Q.2d at 1005. However, the court goes on to say that "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement" (emphasis added). *Id.* The court also notes that "a specification need not disclose what is well known in the art." *Id.* In the specification, Applicant states that the genes that may be characterizing genes in the embodiments of the invention are known in the art and, therefore, are not the "novel" aspects of the invention. Specification, Section 4.2.1. Thus, since genes that may be characterizing genes are well known in the art and are admittedly not novel, the specification is enabling according to *Genentech*.

The Examiner further contends that the specification is non-enabling because the specification allegedly fails to teach specific pathways and phenotypes with which characterizing genes are associated and because the specification does not provide means to isolate these genes or provide these genes in the context of the claims. Office Action, pp. 8-9. Applicant respectfully disagrees. When rejecting a claim under the enablement requirement of 35 U.S.C. § 112 the Patent Office bears the initial burden of setting forth a reasonable explanation as to why it believes the claims are not adequately enabled by the description of the invention provided in the specification. The Examiner must provide sufficient reasons for doubting any assertions in the specification as to the scope of enablement. *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Examiner has not met this burden because he has not provided any references that support his assertion. If the Examiner is relying on any facts within his personal knowledge as a basis for the rejection, he is hereby requested to supply an affidavit specifying with particularity the data supporting the rejection. 37 C.F.R. § 1.104(d)(2).

Even arguing, arguendo, that the PTO has met its burden, Applicant submits that this allegedly prima facie rejection is overcome. The Examiner alleges that the specification is non-enabling because it does not teach the particular phenotypes with which characterizing genes are associated. Section 4.2.1 of the specification discloses non-limiting examples of characterizing genes known in the art that are associated with specific pathways. The specification teaches that, in certain embodiments, the characterizing genes are groups of genes that are expressed in cells of the same or different phenotypes. Specification, p. 7, ll. 6-10; Pub. App. at ¶ 23. The specification also discloses that information about characterizing genes and information regarding phenotypes can be found in public databases, such as the Mouse Genome Informatics Database sponsored by the Jackson Laboratory. Specification, p. 22, ll. 27-31; Pub. App. ¶ 160. As discussed above, one skilled in the art is

presumed to use the information available to him in attempting to make or use the claimed invention and well known subject matter is preferably omitted. See *Northern Telecom,* 15 U.S.P.Q.2d at 1329 and *Hybritech*, 231 U.S.P.Q. at 94. Thus, the specification is enabling.

The Examiner also alleges that the specification is non-enabling because the specification fails to provide the genes and methods of isolating genes in the context of the claims. Office Action, p. 9. The present invention is directed at collections of two or more transgenic animal lines comprising a transgene comprising system genes coding for a selectable or detectable marker that are operably linked to characterizing gene regulatory elements so that the system genes have the same expression pattern as that of the endogenous characterizing gene and methods of making such collections of transgenic animals lines. Specification, p. 2, ll. 12-16; Pub. App. at ¶ 6. The characterizing gene is endogenous to a host cell or host organism or is the ortholog of an endogenous gene. Specification, p. 21, ll. 9-11; Pub. App. at ¶ 154. The particular select population of cells either expresses or does not express the endogenous gene. Specification, p. 21, ll. 11-12; Pub. App. at ¶ 154. By operably linking the expression of a system gene coding for a marker with the characterizing gene so that the expression pattern of the system gene is substantially similar to the expression pattern of the endogenous gene, the present invention provides for easy identification and/or isolation of the cells of interest. Specification, p. 2, ll. 12-18; Pub. App. at ¶ 6. The specification describes genes that may be used as characterizing genes in Section 4.2.1 and system genes in Section 4.2.2 in accordance with the present invention and directs one skilled in the art to databases and other references that provide additional information regarding these genes. These genes and methods of isolating these genes for use in making transgenic constructs are known in the art. In Section 5, the specification also provides an example for creating a transgenic animal line of the invention using BAC clones containing the endogenous genes of interest, *i.e.*, the characterizing genes, as a starting point for the invention. Therefore, the specification provides genes and methods of isolating genes in the context of the claims and is thus enabling.

For the reasons stated above, Applicant submits that the rejection of claims 1-27 and 32-60 under 35 U.S.C. § 112, first paragraph is overcome, and respectfully request that that the rejection be withdrawn.

2. **Specification is enabling for the characterizing gene to regulate the system gene**

The Examiner further alleges that the specification is not enabling because the specification does not provide evidence that the characterizing gene regulates the system gene to have the same expression pattern as the endogenous gene. Office Action, p. 5. The Examiner further cites to several references and alleges that even if the promoter region of a given gene is known, aspects of regulation cannot be determined. Office Action, pp. 6-7. Applicant respectfully submits that the specification fully enables one of ordinary skill in the art to make and use the invention.

As discussed above, the specification teaches that all or some of the regulatory sequence of a characterizing gene is incorporated into the transgene of the invention to regulate the expression of the system gene coding a marker so that the expression pattern of the system gene is similar to the expression pattern of the endogenous counterpart of the characterizing gene. Specification, p. 21, ll. 14-16; Pub. App. at ¶ 154. In particular, the specification teaches that the characterizing gene genomic sequences are preferably in a vector that can accommodate large lengths of sequence, such as cosmids, YACs, and BACs that encompass 50 to 300 kb of sequence. Specification, p. 19, ll. 9-14; Pub. App. at ¶ 149. The larger the sequence the more likely that it will contain the required regulatory sequences of the characterizing gene to direct the expression of the system gene coding sequences in substantially the same pattern as the endogenous characterizing gene. Specification, p. 19, ll. 13-18; Pub. App. at ¶ 149. Vectors with sufficient lengths of the characterizing gene can be identified using methods known in the art. Specification, p. 19, l. 19 to p. 20, l. 8; Pub. App. at ¶ 149. Methods of constructing such vectors are known in the art and the specification provides, by way of example, how to make and use a BAC vector of the invention. See Specification, Section 5. In fact, libraries of BACs containing mouse genomic sequences that can be readily screened are publicly available, as disclosed in the specification, p. 59, ll. 11-30; Pub. App. ¶ 179. The specification also points out that it is within the knowledge of one of skill in the art to determine the sufficient length of the promoter region required to promote transcription are also well known in the art and is described in Alberts *et al.* (1989) in Molecular Biology of the Cell, 2d Ed. (Garland Publishing, Inc.). Specification, p.12, ll. 31-33; Pub. App. at ¶ 122.

The references cited by the Examiner actually support the teachings of the Applicant's specification that methods of making transgene constructs of genes associated with specific regulatory sequences are known in the art and that problems of expression may,

in general, be corrected with larger portions of the characterizing gene regulatory sequences. Applicant, however, does not admit that any of the references cited by the Examiner are prior art. Eid *et al.* (Dev. Dyn., 1993) teaches that transgenic mice generated with various Hoxb-6 gene promoters operatively linked to LacZ reporter gene could not reproduce the regulation of the endogenous Hoxb-6 gene. Office Action, p. 6. Applicant respectfully points out that in Eid *et al.*, the researchers state that the reporter gene (transgene) construct of the Hoxb-6 gene produced part of the expression pattern of the endogenous Hoxb-6 gene and so the study suggested that the larger genomic regions of the Hoxb cluster may be needed to mimic the entire expression pattern of the endogenous gene. Eid *et al.* at p. 205, Abstract, lines 24-36. The Examiner also states that Leinwand *et al.* shows that even if a generalized expression pattern could be generated, additional elements of the promoter fragment appear to be necessary.

All that Eid *et al.* and Leinwand *et al.* disclose is that an insufficient length of the regulatory sequence of the gene was incorporated into the transgene to mimic the expression pattern of the gene. The specification teaches that the transgene of the invention should contain all or a portion of the characterizing gene genomic sequence sufficient to direct the expression of the system gene coding sequence to have the same expression pattern of the endogenous characterizing gene. Specification, p. 59, ll. 4-10; Pub. App. at ¶ 178. As stated previously, making constructs comprising a gene sequence to control the expression pattern of a gene is well known in the art. The specification discloses that the characterizing gene genomic sequences are preferably in a vector that can encompass large lengths of sequence, such as cosmids, YACs, and BACs that encompass 50 to 300 kb, to ensure that the vector contains sufficient regulatory sequences from the characterizing gene to direct expression of the system gene coding sequences in substantially the same pattern as the endogenous gene. Specification, p. 19, ll. 9-14; Pub. App. at ¶ 149. Vectors that have sufficient regulatory sequences of the characterizing gene can be screened using methods known in the art. Specification, p. 19, l. 13 to p. 20, l. 9; Pub. App. at ¶ 149. The specification also provides an example in Section 5 of making and using a BAC vector of the invention. Applicant notes that an invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech*, 231 U.S.P.Q. at 94. Even considerable amount of experimentation is permitted if it is merely routine or the specification provides reasonable amount of guidance and direction to the experimentation. *Ex parte Jackson*, 217 U.S.P.Q. at 807. For these reasons, the specification provides sufficient guidance to one of ordinary skill in the art to construct a transgene of the invention

and determine whether the characterizing gene regulates the expression of the system gene to be substantially the same as the endogenous characterizing gene.

The Examiner also alleges that the specification is not enabling because, although the specification teaches that various homologue or ortholog promoters can be used in the invention, references disclose that the same promoters from different species do not share the same function or expression pattern. Office Action, p. 6. In particular, Examiner cites Thomas *et al.* (Exp. Cell Res., 2000) as teaching that the regulation of osteocalcin from the mouse and human have divergent expression control. *Id.* As stated by the Examiner, in Thomas *et al.*, transgenic mice were generated with human osteocalcin promoter operatively linked to a CAT reporter. *Id.* In Thomas *et al.*, the transgenic model expresses both the expression patterns of the human osteocalcin gene and the mouse osteocalcin gene so that the two genes could be tested in identical environments. Thomas *et al.* p. 395, col. 2, ll. 26-29. The human osteocalcin promoter did not produce the same expression pattern as the endogenous mouse osteocalcin promoter, rather it produced the expression pattern of the endogenous human osteocalcin gene. Thomas *et al.*, p. 395, col. 2, ll. 13-18. Unlike, Thomas *et al.*, Applicant's specification teaches that the characterizing gene is preferably endogenous to the transgenic animal or an ortholog of the endogenous gene (*i.e.*, not from different species in which the expression pattern may differ) and controls the expression of the operably linked system gene to have the same expression pattern of the endogenous characterizing gene. Specification, p. 11, ll. 27-30 and p. 12, ll. 2-5; Pub. App. at ¶ 120 and ¶ 121. Thus, as stated above, the use of specific regulatory sequences to control expression patterns of a certain gene in transgenic animals is known in the art. The specification enables one of ordinary skill to practice the invention, and any experimentation required to practice the invention is routine in the art.

The Examiner further alleges that the specification is not enabling because the behavior of a transgene is affected by how it is delivered. Office Action, p. 7. In support of this, the Examiner cites Linney *et al.* which compares the transgene expression in zebrafish produced by direct injection and retrovirus delivery. *Id.* However, Linney *et al.* states that the expression transgenics by either retroviral vector infection or DNA injection were comparable. Linney *et al.* at p. 214, col. 1, ll. 20-24. In addition, Linney *et al.* discloses that it is unknown whether transcriptional signals in the flanking retroviral long terminal repeats ("LTRs") impact the developmental regulation of the internal regulatory sequences in a retroviral vector. Linney *et al.* at p. 214, col. 1, ll. 17-20. Applicant also respectfully points out to the Examiner, that, while the predictability of the art can be considered in determining

whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). Even if, as the Examiner alleges, the level of a transgene varies depending on how it is delivered, effective methods of delivering transgenes are well known in the art and include methods described in Sections 4.3, 4.4, and 4.5 of the specification, thus the specification is enabling. Testing for expression of transgenes is also known in the art and one method is described in Section 5 of the specification. Thus, variability in expression caused by different modes of delivering transgenes should, in most cases, be overcome by routine experimentation. Therefore, the specification is enabling to one of skill in the art to practice the invention.

For the reasons stated above, Applicant respectfully requests that the rejection of claims 1-27 and 32-60 based on 35 U.S.C. § 112, first paragraph be withdrawn.

3. <u>Specification is enabling even though transgenic art is unpredictable</u>

The Examiner alleges that the specification is not enabling because the physiological art is unpredictable. Office Action, p. 8. While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. The court of Custom and Patent Appeals specifically cautioned that the unpredictability of the result of an experiment should not be the basis of concluding that the amount of experiment. The court stated in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976) that if § 112, first paragraph required the disclosure to "provide guidance which will enable one skilled in the art, to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained....then all 'experimentation' is undue since the term 'experimentation' implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act." *Id.* at 219 (emphasis in the original).

The Examiner contends that the art of transgenic animals is unpredictable because transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species, as exemplified by Hammer *et al.*, Mullins *et al*, and Wall *et al.* Office Action, p. 8. In addition, the Examiner alleges that since the specification does not disclose nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene or that the animal produced will be viable or capable of producing progeny. *Id.* Applicant respectfully points out that the

references cited by the Examiner involve the use of transgenes comprising regulatory sequences from species other than the host species or designed to overexpress or under express an endogenous gene product whereas the Applicant's specification teaches that the characterizing gene which regulates the expression pattern of the system gene is preferably endogenous to a host cell or host organism or is an ortholog of an endogenous gene. Office Action, p. 8; Specification, p. 21, ll. 9-11; Pub. App. at ¶ 154. The transgene of the present invention is not designed to increase or decrease significantly the expression of the endogenous characterizing gene or other endogenous genes in the host animal, but rather it is designed to induce the expression of a detectable or selectable marker in cells that express the endogenous characterizing gene. Since the expression of the transgene of the invention does not need to alter the physiology of the host animal, but simply mark cells for isolation and identification, transgenic animals of the invention are likely to be viable and/or capable of producing progeny and their phenotype is predictable. Viability and phenotypic issues may, thus, in general, be overcome with routine experimentation.

The references cited by the Examiner disclose the use of regulatory sequences from species other than the host species. Office Action, p. 8. The specification teaches that if the sequence of the characterizing gene of one species is known and the counterpart gene from another species is desired, probes should be designed based on the known sequence using routine methods in the art. Specification, p. 17, l. 34 to p. 18, l. 3; Pub. App. at ¶ 143. By way of example and not limitation, the specification discloses different methods known in the art to design probes based on the known sequence. Specification, p. 18, l. 4 to p. 19, l. 2; Pub. App. at ¶ 144-147. Methods of producing viable transgenic animals using vectors containing a transgene and other vehicles are well known in the art and also disclosed in the specification. Specification, Sections 4.3, 4.4, and 4.5. As stated above, since transgenic mice of the present invention have cells expressing a marker in cells expressing an endogenous characterizing gene, animals of the present invention produced by methods known in the art, will more likely be viable and fertile.

Although the results of the cited references suggest some variability of transgene expression in different species of transgenic non-human animals and there may be a possibility that some transgenic animals produced may not be viable or produce progeny, Applicant respectfully points out that transgenic animals have been obtained using methods routine in the art and as stated above, enablement does not require certainty of the results of routine experiments. See *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976). However, the

skilled artisan, with routine experimentation could obtain the claimed collection of transgenic animals.

Lastly, the Examiner alleges that the specification is not enabling because the use of IRES sequence for multiple transgene expression does not necessarily provide for controlled or regulated expression, for example, as taught by Jankowsky *et al.* Applicant respectfully submits that Jankowsky *et al.* is not contrary to what the specification teaches, that is, an IRES operably linked to the system gene coding sequence can direct the translation of the system gene. See Specification p. 15, ll. 11-16; Pub. App. at ¶ 131. As stated by the examiner, Jankowsky *et al.* discloses that the use of an IRES sequence to control the expression of the APP gene and PS1 gene resulted in expression patterns that differed from expression patterns produced by coinjection of a construct an APP gene and a construct of a PS1 gene. Office Action, p. 9 and Janowsky *et al.*, p. 157, abstract. However, Janowsky *et al.* also teaches that the use of an IRES sequence to control the expression of the APP gene and the PS1 gene resulted in both genes having the same expression pattern. Jankowsky *et al.*, p. 161. col. 2, ll. 54-55; Pub. App. at ¶ 131. This is precisely the outcome desired in the present invention, *i.e.*, similar expression of the system gene and endogenous characterizing gene. The present invention is directed at collections of two or more transgenic animal lines comprising a transgene comprising system genes coding for a selectable or detectable marker that are operably linked to a characterizing gene so that the system genes have the same expression pattern as that of the endogenous characterizing gene and methods of making such collections of transgenic animal lines. Thus, in the present invention, the endogenous characterizing gene and the system gene are supposed to have substantially the same expression pattern. The specification teaches that an IRES can be used in certain embodiments of the present invention to direct translation of the system gene to have the same expression pattern as the endogenous characterizing gene and discloses several references to guide one of ordinary skill in the art. Specification, p. 15, ll. 9-12; Pub. App. at ¶ 125. Applicant also notes that Janowsky *et al.* discloses transgenic mice with mosaic expression, that is, expression of multiple genes that have physiological effects on the host, whereas Applicant's invention is intended not to alter the physiology of the host, but rather mark the cells of the host for expression of the endogenous characterizing gene. In addition, as discussed above, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. See *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

Therefore, the specification is enabling for the use of IRES sequences in various embodiments of the invention.

For the reasons stated above, Applicant respectfully requests that the rejection of claims 1-27 and 32-60 under 35 U.S.C. § 112, first paragraph be withdrawn.

C. Claims 1-27 and 32-60 are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 1-27 and 32-60 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Office Action, p. 10. In particular, the Examiner has pointed out that Claim 1 and 32 are unclear and indefinite in the recitation of "an expression pattern that is substantially the same" because the metes and bounds of "substantially" is not clearly set forth. *Id.* Applicant respectfully directs the Examiner's attention to the specification p. 13, l. 33 to p. 14, l. 1 where the specification states that "[b]y 'substantially the same expression pattern' is meant that the system gene coding sequences are expressed in at least 80%, 85%, 90%, 95%, and preferably 100% of the cells shown to express the endogenous characterizing gene by *in situ* hybridization." The patentee can be his own lexicographer as long as the terms are defined and the terms are used in a consistent manner. *United States Surgical Corp. v. Ethicon, Inc.*, 41 USPQ2d 1225, 1236-1237 (Fed. Cir. 1997), cert. denied, 118 S. Ct. 369 (1997). Therefore, the specification clearly sets forth the metes and bounds of "substantially" are clearly set for claims 1 and 32 are definite under 35 U.S.C. § 112, second paragraph.

The Examiner also alleges that independent claims 1 and 32 require that the transgene is not in the same location as the endogenous gene and thus claims 7 and 38 are confusing in the recitation of "that is not operably linked to a coding sequence of said characterizing gene." Office Action p. 11. The Examiner further alleges that there are no limitations in claims 1 and 32 that indicate the presence of the characterizing gene. *Id.* Applicant respectfully disagrees.

Claims 1 and claims 32 are directed at collections of two or more transgenic animal lines and methods of making such collections comprising transgenes comprising (a) first sequences coding for a selectable or detectable marker protein operably linked to (b) a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene. Thus, the presence of the characterizing gene is a limitation of claims 1 and 32.

Claims 7 and 38 depend on claims 1 and 32, respectively, and recite that the "first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene." In other words, claims 7 and 38 are directed to collections of two or more transgenic animal lines comprising transgenes and methods of making such collections wherein the transgene comprises of (a) first sequences coding for a selectable or detectable marker protein (claims 1 and 32) that is operably linked to an IRES sequence (claims 7 and 38) and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences (claims 1 and 32), but not operably linked to the IRES sequence that is linked to the first sequences (claims 7 and 38). Therefore, claims 7 and 38 are clear and definite.

For the reasons stated above, claims 1-27 and 32-60 are definite under 35 U.S.C. § 112, second paragraph and the rejection should be withdrawn.

D. <u>Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56, and 60 are patentable over U.S. Patent No. 6,353,151B1 to Leinwand *et al.*</u>

Claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 60, and 60 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,353,151 to Leinwand *et al.* ("Leinwand"). Applicant respectfully disagrees.

35 U.S.C. § 102(e) states that a person is entitled to a patent unless his invention was described in a patent granted on an application for patent by another before the invention by the applicant for patent. For a rejection under § 102 requires that "each and every limitation of the claimed invention be disclosed in a single prior art reference." *In re Paulsen*, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994).

Claims 1 and 32 disclose a collection of two or more lines of transgenic animals and methods of making such collections wherein each transgenic animal comprises a transgene comprising first sequences coding for a selectable or detectable marker protein operably linked to regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene so that the expression pattern of the first sequence is substantially the same as the expression pattern of the endogenous characterizing gene where each strain of the collection has a different characterizing gene. In other words, claims 1 and 32 are directed at collections of two or more animal lines where each line has a system gene regulated by a different characterizing gene. In contrast, Leinwand only discloses use of the regulatory sequences of a single gene, that is a heart tissue specific

promoter, and does not disclose a collection of lines of transgenic animals with transgenes having regulatory sequences from different characterizing genes or the methods of making such collections. Leinwand at col. 4, ll. 35-38. Therefore, Leinwand does not disclose each and every limitation of the claimed invention and does not anticipate Applicant's present invention. Claims 2, 14, 18, 19, and 22, which are dependent on claim 1, and claims 33, 45, 49, 50, 53, 56, and 60, which are dependent on claim 32, are also directed to collections of lines of transgenic animals and methods of making such collections, therefore Leinwand also does not anticipate these claims. For the reasons stated above, Applicant respectfully requests that the rejection under 35 U.S.C. § 102(e) of claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56, and 60 be withdrawn.

E. <u>Rejection for Double Patenting should be held in abeyance</u>

Claims 1-27 and 32-60 are provisionally rejected under 35 U.S.C. § 101 as unpatentably over claims 1-27 and 32-60 of co-pending Application No. 10/077,025. Applicant respectfully requests that the double-patenting rejection be held in abeyance until the present claims are indicated to be allowable but for the double-patenting rejection.

V. CONCLUSION

It is believed that no fee is due in connection with this amendment (other than for the Extension of Time submitted separately herewith). However, should the Patent Office determine that a fee is due, please charged the required amount to Pennie and Edmonds LLP Deposit Account No. 16-1150.

Applicant believes that each ground for rejection of the pending claims has been successfully overcome. According, Applicant respectfully requests that the following rejections be withdrawn: (1) rejection of claims 1-27 and 32-60 under § 112, first and second paragraphs, (2) rejection of claims 1, 2, 14, 18, 19, 22, 32, 33, 45, 49, 50, 53, 56, and 60 under 35 U.S.C. § 102(e), and (3) rejection of claims 1-27 and 32-60 under 35 U.S.C. § 101.

Applicant submits that the entire application is now in condition for allowance, early notice of which would be appreciated. The Examiner is invited to telephone the undersigned should any issues remain.

Respectfully submitted,

Dated: June 30, 2003

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Enclosures